VIRUSES AND INDOOR AIR POLLUTION*

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The natural occurrence of air pollution by microorganisms and of human disease from inhaling these organisms is established. Microbiologic and epidemiologic data document airborne transmission of a large number of bacteria and fungi, including psittacosis, Q fever, brucella, anthrax, certain fungi, legionella, and tuberculosis. Among these, quantitative data relating to air pollution and transmission are available only for tuberculosis and Q fever, and only one, tuberculosis, involves person-to-person transmission.

Microbiologic and epidemiologic data have shown that a number of viruses may contaminate the air of rooms and be capable of initiating disease in those who inhale them. However, with the exception of lymphocytic choriomeningitis virus, all are viruses transmitted from person to person. Quantitative data concerning air pollution and transmission is available for only one virus, coxsackie virus A type 21. These data suggest that certain circumstances and certain respiratory viruses involve transmission by the airborne route; they will be summarized in this report. In addition to respiratory viruses, evidence for other viral diseases transmitted by the airborne route will be cited; these include viruses of historical as well as current significance.

VIRUSES TRANSMITTED BY AIR

Available evidence indicates that a number of viruses that infect humans can be transmitted by the airborne route (Table I). Among them

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TABLE I. HUMAN VIRAL DISEASES THAT ARE TRANSMITTED BY THE AIRBORNE ROUTE

Smallpox	Influenza
Chicken pox	Adenovirus 4 and 7
Measles	Coxsackie A21
Rubella	Lymphocytic choriomeningitis

are the commonest infections of mankind both historically and currently. All are transmitted from an infected to a susceptible person except for lymphocytic choriomeningitis virus which is shed into the urine by chronically infected animals. Outbreaks among vivarium workers have been traced to changing and cleaning cages occupied by infected hamsters, and the common source nature of the outbreaks indicates airborne spread.[1] Sporadic cases of lymphocytic choriomeningitis disease also occur in the home and are attributable to viruses shed by chronically infected mice. Although the route of acquisition of infection in the home is uncertain, air contamination is a prime possibility.

The human viral disease receiving most attention historically for transmission by the airborne route has been measles. Wells, during the 1930s and 1940s, dissented from the popular belief that infectious diseases were transmitted by contact and this led him to focus study on measles. The rapid spread and high attack rates of measles in school classrooms suggested airborne transmission. Wells and his wife proved that this was the case by demonstrating reduction in measles attack rates in schools where ultraviolet air disinfection was used.[2,3] More recently, an epidemic among an immunized population of school children in New York State exhibited the characteristics of airborne spread and indicated the power of airborne transmission in a highly immune population.[4]

Rubella (German measles) attracted major attention because of recognition that congenital abnormalities occurred in children of women infected during pregnancy. The relatively recent availability of vaccines for rubella provided most of the stimulus for intensive study of its epidemiology. Although Langmuir emphasizes that the epidemiology is still poorly understood, increasing evidence is available that rubella is primarily transmitted by the airborne route.[5] The rapidity of epidemics with high attack rates in English boarding schools could only be explained by airborne spread.[6] Moreover, significant attack rates among highly immune military populations are reminiscent of the measles epidemic in an immunized school population described above.[7] Such an occurrence requires almost unavoidable exposure to virus, a circumstance characteristic of air contamination of a room containing susceptible subjects.

The prevailing concept that smallpox is transmitted by contact was contradicted by an outbreak in a hospital in West Germany in 1970.[8] An imported case went unrecognized for a brief period and led to 17 secondary cases, all traceable to exposure to air from the room which contained the infected patient. The significance of this route of transmission versus a contact route in countries where smallpox was endemic for centuries is unknown, but with the eradication of smallpox the question has become moot.

Chicken pox (varicella) is considered by many to be the most contagious of infectious diseases. Anecdotal reports of infection acquired by mere presence in the room with a case and the high attack rates among groups of susceptible young children after a common exposure provided the basis for the common belief that most cases are acquired by the airborne route. This belief was recently supported by a hospital outbreak where 15 secondary cases were traced to a hospitalized child with chicken pox pneumonia.[9] Of interest is the high attack rate (9/10) among children in the room across the hall, which, because of a nonfunctioning ventilator, acquired the greatest airflow from the room containing the infected case. Numerous similar outbreaks in hospitals where contact could not have occurred are unpublished, but again the relative significance of contact versus airborne spread in various natural circumstances is unknown.

Mumps has also been suggested to be transmitted by the airborne route, but the slow spread and relatively poor communicability when compared to measles and chicken pox have caused most to believe that mumps is primarily transmitted by a contact route.[10]

The respiratory viruses, causes of common colds, sore throats, bronchitis, and influenza, are major candidates for transmission by the airborne route. As part of a program to study these agents in normal volunteers, we developed an early interest in elucidating the natural means of transmission of these agents. We approached this question by examining a model infection quantitatively in normal adult volunteers. The virus we selected was coxsackie virus A type 21. It had caused epidemics of acute respiratory disease in the military, but was apparently not a common infection in civilian populations, so that 40% of persons lacked serum antibody and were considered susceptible.

QUANTITATIVE STUDIES WITH COXSACKIE A21

Studies designed to examine quantitatively the different events required for airborne transmission were undertaken by us during the 1960s in collaboration with the United States Army Biological Laboratories at Fort Detrick, Md. We reasoned that infected individuals must produce small particle aerosols containing virus and that these aerosols should result in enough room-air contamination to infect susceptible individuals inhaling that air. We examined this sequence in a quantitative manner.

Virus in sneezes and coughs. During the three- to five-day period of illness and when quantities of virus in respiratory secretions are maximal, stimulated sneezes and simulated coughs produced by volunteers who had been inoculated with coxsackie A21 were collected in weather balloons.[11] Assays for virus were performed separately on air evacuated into impingers and of liquid rinses of the balloon wall. As shown in Table II, 52% of sneeze and 39% of cough samples contained the virus. Thirty percent of the air samples were positive for both events, and mean quantities of virus in samples were 30 $TCID_{50}$ for coughs and 60 $TCID_{50}$ for sneezes. This occurred despite the fact that other studies on particles produced by these events revealed that 20-fold or greater numbers and particle volumes were produced by sneezes.[12] An extensive testing of air expired during breathing was performed, and those tests failed to detect infectious virus.[11]

When examined for factors relating to release of virus in sneezes or coughs, it was found that a sneeze sample was likely to be positive if the volunteer had nasal obstruction and discharge, whereas a positive cough sample was related only to the quantity of virus in secretions, and this relationship was only for the air phase.

Virus in room air. The contribution of coughing, sneezing, and other expiratory events to room air contamination was evaluated by sampling about 70% of the air of rooms containing infected volunteers after a period of two hours with no ventilation. For this purpose, a sampler capable of sampling 10,000 l./min. of air was used.[12] Table III shows the results of testing 30 samples. Fourteen contained virus, and the frequency of positive samples increased with increasing quantities of virus in respiratory secretions. Because both positive cough air samples and

TABLE II. VIRUS RECOVERY FROM PARTICLES IN COUGHS AND SNEEZES PRODUCED BY VOLUNTEERS INFECTED WITH COXSACKIEVIRUS A TYPE 21

Phenomenon	*No. tested*	*% positive*	*Source*	*% positive*
Sneeze	58	52	Air*	30
			Wall†	45
Cough	61	39	Air*	30
			Wall†	20

*Assay of Shipe impinger collection of particles suspended in air in balloon
†Assay of 10-ml liquid rise of balloon wall

TABLE III. RELATION OF VIRUS QUANTITY IN RESPIRATORY SECRETIONS TO VIRUS IN ROOM AIR SAMPLES

	Air sample	
Mean (3 vol.) virus quantity in secretions	*No. tests*	*No. positive*
10-30*	5	1
30-100	11	2
100-300	5	4
300-1,000	6	4
1,000>1,000	3	3

*Expressed as $TCID_{50}$ per milliliter of secretion

room air samples were related to the concentration of virus in secretions, a relationship between virus in cough air and room air was sought. When analyzed by room, it was found that presence of virus in cough air samples from volunteers occupying a room was significantly related to recovery of virus from the air of that same room on the same day.[11] No such relationship was detected for sneezing. This is not surprising because coughing occurred frequently, whereas sneezing was infrequent. We concluded that cough was a major event for producing air contamination, a finding reminiscent of the apparent significance of cough in transmission of tuberculosis.[13]

Infectivity of coxsackie A21 for man. The relative infectivity of coxsackie A21 for the upper and lower respiratory tract of man was determined in conjunction with the studies just described. A range of doses of two separate strains of coxsackie A21 were given to serum antibody negative volunteers. The calculated 50% human infectious dose (HID_{50}) for small particle inoculations corresponded to 28 and 34 $TCID_{50}$, and large particle aerosol (15 μ particles) and nose drop inoculations with one strain corresponded to 32 and 6 $TCID_{50}$, respectively.[11] Doses comparable to those required to infect man were detected in single cough and sneeze samples and were exceeded by the amount of virus recovered in room air samples.

Airborne transmission of coxsackie A21. To determine whether air contamination with coxsackie A21 was sufficient to produce airborne transmission, we evaluated the infectiousness of coxsackie A21 among susceptible volunteers separated from infected volunteers by a double wire barrier that prevented contact transmission.[14] In that study 10 infected volunteers were housed on one side of a barracks; eight of these developed clinical illness, and testing of cough and sneeze samples on four separate days indicated they were capable of generating infectious aerosols. Samples of air using the same large volume air sampler used earlier revealed contamination of air throughout the barracks on at least four separate occasions. Among 19 susceptible volunteers on the other side of the wire barrier, five infections occurred three days after the first positive air sample, and 10 more occurred four days after a second positive sample. Thus, airborne transmission was proved. Based on calculated recoveries and room size, it was estimated that there was at least 1 $TCID_{50}$ per 100 liters of room air, although it is probable that larger amounts were actually present. Using respiratory minute volumes and an HID_{50} of 30 $TCID_{50}$ for calculations, it would require about four hours for inhalation and retention of an infectious dose.

THE RESPIRATORY VIRUSES

The quantitative data derived from the coxsackie A21 experience identified three features of respiratory viral disease that would imply airborne transmission: rapidly progressive natural epidemics in a barracks type situation, moderate to severe cough as a major feature of natural disease, and a high degree of susceptibility of the lower respiratory tract to virus.

Available information indicates that epidemic coxsackie A21 and adenovirus type 4 or 7 disease among military populations and epidemic influenza among all populations results primarily from air contamination with virus, whereas available information indicates that rhinoviruses, the most prevalent causes of common colds, are transmitted primarily by contact. There is insufficient information for conclusions regarding the major mechanism of transmission of other respiratory viruses, although it has been suggested that transmission of respiratory syncytial virus to pediatric ward personnel requires contact with infected infants.[15] The prevailing concept, although unsupported by objective evidence, is that other respiratory viruses are transmitted primarily by contact.

Adenoviral disease in military personnel. A major disease problem among military personnel in the past has been acute febrile undifferentiated respiratory disease. It has been associated most prominently with types 4 and 7 adenovirus infection. The disease is characterized by diffuse involvement of the respiratory tract, and tracheobronchitis with prominent cough is common. The cough with an infection that commonly occurs in barracks type situations suggests that naturally occurring adenoviral disease in the military is primarily transmitted by the airborne route. In this regard, adenovirus has been recovered from the air of barracks containing infected persons.[16]

In our studies, an HID_{50} for adult volunteers with small particle aerosol inoculation corresponded to 0.5 $TCID_{50}$, whereas the HID_{50} by nasal drops was 9 $TCID_{50}$.[11,17] This 20-fold difference indicates greater infectivity for the lower respiratory tract. Moreover, only the small particle aerosol inoculations produced a pattern of disease similar to that described for naturally occurring infections. Thus, evidence is compelling that epidemic acute respiratory disease among military populations caused by adenovirus is a consequence of inhalation of airborne virus.

Influenza. Evidence indicates that epidemic influenza is primarily transmitted by the airborne route. Explosive outbreaks are common in such crowded circumstances as military barracks, prominent cough resulting from tracheitis is characteristic of the clinical disease, studies in volunteers indicate a low infectious dose for small particle aerosol inoculations, and the natural disease is better reproduced in volunteers by small particle inoculation than by nasal drops.[18,19] Early lower respiratory tract involvement during naturally occurring influenza suggests that infection is initiated at this site, and deposition of virus in the lower respiratory tract would require small particle aerosol inoculation.[20] Finally, the recent demonstration of an influenza outbreak on an airliner in Alaska proved that airborne transmission can occur.[21] Thus, available evidence is compelling for a paramount role for airborne transmission of epidemic influenza. This conclusion is supported by a series of elegant studies by Shulman and Kilbourne in mice, where it was conclusively shown that transmission between mice occurred only by the airborne route.[22]

Rhinovirus common colds. The most common viruses isolated from people with naturally occurring common colds are rhinoviruses. Gwaltney and Hendley have provided experimental evidence that all conditions required for contact transmission of rhinovirus common colds are fulfilled.[23] These conditions include contamination of fingers and environmental objects, survival of virus in this circumstance, and induction of infection by rubbing the eyes and "picking the nose" with fingers contaminated by virus. Moreover, Gwaltney, D'Alessio, and Couch were unable to demonstrate airborne transmission in experimental circumstances.[23] Thus, evidence shows that rhinoviruses are transmitted primarily by contact, and, in addition to experimental evidence, epidemiological evidence also favors contact transmission.

Other respiratory viruses. Naturally occurring infection with respiratory syncytial virus, the parainfluenza viruses, and adenovirus types 1, 2, 3, 5, and 6 commonly produce severe respiratory disease in infants and small children. Moreover, they also commonly produce upper respiratory disease in older children and adults. Although definitive evidence is not available to identify the manner of transmission of naturally occurring infections, the prevailing concept is that these viruses are primarily transmitted by close contact.

Approaches To Control Of Airborne Viral Disease

Theoretical possibilities for control of airborne viral diseases described are to reduce air contamination by infected persons, to inactivate or to remove the airborne virus, or to render the potential susceptible person resistant to the virus. Quarantine has been the only approach used to reduce air contamination by viruses, and it has been notably ineffective for the diseases enumerated. Although chemotherapy of infected people might reduce the amount of virus they disperse into the air, effective antiviral agents for this purpose are not yet available. Because cough appears to be the major event producing air contamination by respiratory viruses, cough suppressants might reduce production of aerosols; such a possibility has not been tested, but a detrimental effect would have to be considered from reduced clearance of microorganisms and increased susceptibility to secondary bacterial infection.

Inactivation of virus or removal of the viral aerosol would effectively block airborne transmission. While inactivation by ultraviolet light was initially effective for measles, other trials produced disappointing results. Similar attempts at dust control and ultraviolet inactivation of microorganisms in military barracks met with limited success.[24] Assuming that the approach is capable of success, then the explanation for disappointing results probably lies in inability to sterilize all locations frequented by susceptible people. Although improved ventilation would effectively prevent airborne transmission, the cost of such an approach is reportedly too great.[25] Inactivation of virus in air is worth continued consideration; given adequate study and more uniform application, a beneficial effect might be forthcoming.

The approach that has been extraordinarily effective in control of virus disease is vaccination to render susceptible individuals resistant to the virus. This approach eradicated smallpox, relegated measles and mumps to a minor problem, brought about great reduction in congenital rubella in the United States, and prevented adenoviral epidemics in military populations. Two of the viruses cited as transmitted by the airborne route, lymphocytic choriomeningitis and coxsackie A21, are of minor significance and require very little attention. However, the two remaining viruses, chicken pox and influenza, are major causes of morbidity in man. Because of the omnipresence of chicken pox virus and the more serious disease seen in adults experiencing primary infection, it does not seem wise to attempt environmental control of chicken pox at the present time. However, the possibility that environmental control would reduce the severity of influenza epidemics is worthy of consideration. Both a vaccine (inactivated influenza virus vaccine) and a chemotherapeutic agent (amantadine) are available for influenza, but neither is recommended for use in the United States in a manner that would affect morbidity during epidemics. The extent of morbidity and mortality that accompany influenza epidemics indicates a need for control.

The Problem Of Influenza

For the past seven years we have been performing surveillance of influenza in the city of Houston, Texas, and examining its occurrence in a group of families. An epidemic with an influenza virus has occurred each winter since surveillance began in 1974. A summary of the experience from 1974 to 1978 (Glezen, unpublished data) revealed that approximately 25% of all people with febrile respiratory disease who sought medical care during that four-year interval were infected by an influenza virus. Estimates indicated that 18%, or more than 300,000 people in the country, sought medical care during the A/Victoria epidemic in 1976 and 5 to 12% sought care during the other epidemics.[26] Accurate estimates of morbidity are lacking for the country as a whole, but it seems likely that experience elsewhere is similar to that in Houston.

Data substantiating influenza as a cause of death are available for the United States as a whole. In a recent careful analysis, an average of 13,000 excess deaths attributable to influenza occurred each year for the years 1968 to 1977.[27] Glezen, in a hospital survey of the A/Victoria epidemic in Houston, found that the death rate of patients admitted to hospitals with pneumonia or influenza during the epidemic period was threefold greater than reported on death certificates (unpublished data). Thus, even the significant excess mortality reported by the Centers for Disease Control appears to underestimate the number of deaths attributable to influenza.

The highest attack rates of influenza during an epidemic are in the five to 19-year-olds. In three successive epidemics in Houston, the highest percentages of isolates during the early weeks of the epidemic occurred in school-age groups.[26,28] During later phases of the epidemic, isolation rates in school-aged groups decreased while rates in preschool and older people increased. Similarly, a rise in school absenteeism and admissions of pneumonia patients to pediatric hospital wards preceded a rise in industrial absenteeism, admissions of pneumonia patients to adult hospital wards, and deaths attributable to pneumonia or influenza. This supports the contention that epidemics of influenza begin among school-age populations. Data for initiation of influenza epidemics among school-age children was also provided for Asian influenza in 1957 and for Hong Kong influenza in 1968.[29,30]

When families in the Houston Family Study were evaluated for factors relating to occurrence of influenza within the family, the presence of a child in school or day care was the most important determinant of the occurrence of influenza in the home.[31] Taken collectively, these various data provide strong evidence that epidemic influenza begins in classrooms and spreads from there to the community at large.

New approaches to control influenza are needed, and these data indicate they should focus on school-age children. Because they appear to be disseminators to the community, a reduction in their infection rate should reduce the magnitude of community epidemics. Safe and effective vaccines and antivirals are one approach toward this goal; reduction of airborne spread constitutes another.

Concluding Comments

Airborne transmission of human viral disease is essentially an indoor event. Clear examples of this have been described and may be considered as having resulted from inhalation of air contaminated with infectious virus. The number of viruses shown to transmit in this way has grown with time, whereas the number of viruses proved to transmit by contact is short. The notion prevails that failure to demonstrate or to prove airborne transmission indicates that the virus must be transmitted by other means, usually contact, but this is not the case. The relatively crude techniques available to sample and to sterilize air suggest that conclusions from negative studies of airborne transmission should be phrased "failed to demonstrate airborne transmission" rather than "does not transmit by the airborne route." Further, only when the test situation has been shown to permit airborne transmission can the lack of infection after some intervention be considered as definitive.

The notion also prevails that airborne transmission must of necessity produce "common source" rapid outbreaks and that slowly progressive disease must represent contact transmission. The attack rate among a group of people exposed to contamination in a room will be a consequence of the number of infectors producing aerosol, the number of susceptibles in the room, the degree of ventilation, the density of people, and the temperature and relative humidity (which affects viral survival in air) of the room. Alteration of those factors which influence level of air contamination so that a threshold concentration exists would result in a low attack rate. This in turn would provide a second generation of infectors, which would perpetuate an outbreak, and so on in sequence until the number of susceptible individuals was too low to maintain the threshold of air contamination. Although plausible, proof of such an occurrence would be extraordinarily difficult.

Among the viruses for which prevailing evidence supports airborne transmission, only chicken pox and influenza currently occur at a high frequency and lack effective control programs. Because of uncertain and possibly undesirable consequences of delaying infection with chicken pox, only influenza needs effective control. Prevailing evidence indicates that community epidemics of influenza begin in the classroom. Prevention of the spread of virus at this site might effectively reduce the severity of influenza epidemics in the community. The magnitude of the health problem attributable to influenza indicates that any feasible approach that might reduce the severity of epidemics is worthy of pursuit.

Questions and Answers

DR. BERNERD BURBANK (McGraw-Hill): You did not mention mumps. That is not transmissible by air?

DR. COUCH: Mumps has been reported in outbreaks that suggest transmission by the airborne route. However, if one considers all the information available on mumps, the attack rate, the nature of spread, and descriptions of specific epidemics, then one has to conclude that it is primarily transmitted by a contact route. Lacking definitive evidence that it is also transmitted by the airborne route, I took it off my list. I suspect, based on some of the available data, particularly from the military, that it has, on occasion, been transmitted by the airborne route.

DR. BURBANK: Viral hepatitis, type A, is transmitted by ingestion, more or less. I would like to hear you say, if you can, that there is no evidence that it is transmitted by air.

DR. COUCH: To my knowledge, there is no evidence that hepatitis A is transmitted by the airborne route. As you know, the major consideration for airborne transmission of hepatitis was for hepatitis B in hospitals, blood banks, dialysis units, etc. Significant efforts were made to find hepatitis B antigen in air and on surfaces and to relate findings to transmission. Those studies, to my knowledge, yielded no data suggesting airborne transmission so I think we can conclude that hepatitis B is rarely, if ever, transmitted by the airborne route. I don't know of specific studies on hepatitis A, but I believe that it is not transmitted by the airborne route.

DR. BURBANK: The differentiation between contact and aerosol or air transmission is not quite clear to me. I get the idea that if one had the virus in the air here and piped it into the next room, somebody could catch it from breathing that air.

DR. COUCH: Perhaps I should have provided that distinction initially. Technically, I think the aerobiologists would say that if air is involved, it is airborne transmitted; if air is not involved then it must be contact transmitted. I would prefer to take the epidemiologists' definition, and that is that contact transmission is a transmission method that requires close contact, i.e., either direct or indirect contact through a fomite, a surface, or some other intermediary.

All those methods have in common deposition of the virus in the nasopharynx. Now, if you are within three feet of me and I sneeze on you, the majority of the sneeze is in particles with relatively large volumes; they are heavy and will fall immediately to the floor. You would only get infection with these particles if you were close to me. Even though deposition of these particles in your nasopharynx would be airborne transmission, I would like to consider that as contact transmission because you had to be close to me. For airborne transmission, I prefer to consider only small particles that, for the most part, are less than 5 microns; we speak of droplet nuclei being 2 to 4 microns, but particles are not restricted to that range. At any rate, they are small enough to remain airborne and follow the currents of air. As you suggested, I can cough here and infect a person in the back of the room. That is airborne transmission — truly involving air as a major component of transmission. I would like to reserve within three feet, even though it involves air, for contact transmission.

DR. BURBANK: If you are three feet away and you cough or sneeze and I breathe in, you call that contact, right?

DR. COUCH: Yes. The reason is that there is so much inertial force in the large particles that I have to force them directly to you; they have to be big, heavy particles. When small particles enter the air, air creates enough resistance so that they cannot reach you. These particles follow air flow.

MR. STEPHEN WILDER (Sierra Club): I am not a doctor. The doctors I see on television often wear surgical masks. Are they of any use in real life?

DR. COUCH: In terms of preventing airborne transmission or airborne infection with the small particles, they are of limited benefit. The only way in which one can completely prevent this with any certainty is to use something like the filters that coal miners use. I have seen some of these masks and they truly filter the air. The surgical mask removes a lot of the dust which I got in my air sampler and maybe some of the larger particles, such as allergens, but they are of limited benefit for small particles.

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